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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,810	04/08/2005	Matthew Lee Brown	PU4807USW	7741

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GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY, MAI B475
FIVE MOORE DR., PO BOX 13398
RESEARCH TRIANGLE PARK, NC 27709-3398

EXAMINER	
KOSACK, JOSEPH R	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 04/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/530,810	BROWN ET AL.	
	Examiner	Art Unit	
	Joseph Kosack	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,22-42 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,22-42 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/08/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-14, 22-42, and 44 are pending in the instant application.

Election/Restrictions

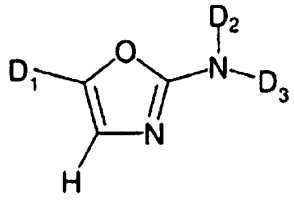
Applicant's election with traverse of the compound of Example 178 on page 153 of the specification in the reply filed on February 16, 2006 is acknowledged. Applicant's arguments were considered, but were not found persuasive.

The requirement is still deemed proper and is therefore made FINAL.

Status of the Claims

Claims 1-14, 22-42, and 44 are pending in the instant application. Claims 1-14 (in part), 22-42 (in part) and 44 (in part) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. The withdrawn subject matter is patentably distinct from the elected subject matter as it differs in the structure and element and would require separate search considerations. In addition, a reference, which anticipates one group, would not render obvious the other.

Pursuant to Applicant's election of a species, the scope of the invention will be limited to the following substitutions of the base structure



where:

- D_1 and D_2 are phenyl groups substituted as defined;
- All other substituents are as defined;

As a result of the election and the corresponding scope of the invention defined supra, the remaining subject matter of Claims 1-14, 22-42, and 44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions. The withdrawn compounds contain varying functional groups such as pyrimidinyl, piperidinyl, imidazoyl, pyrrolidinyl, etc, which are chemically recognized to differ in structure and function. This recognized chemical diversity of the functional groups can be seen by the various classification of these functional groups in the U.S. classification system, i.e. class 544 subclass 244(+) (diazines), class 546 subclass 184(+) (piperidines), 546 subclass 249(+) (pyridines), etc. Therefore the subject matter which are withdrawn from consideration as being non-elected subject matter differ materially in structure and composition and have been restricted properly a reference which anticipated but the elected subject matter would not even render obvious the withdrawn subject matter and the fields of search are not co-extensive.

Priority

The claim to priority as a 371 filing of PCT/US03/33317 filed on October 10, 2003 which claims priority to US Serial Number 60/417,548 filed on October 10, 2002 has been granted in the instant application.

Information Disclosure Statement

The Information Disclosure Statement filed on April 8, 2005 has been considered fully by the Examiner.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: 1,3-Oxazole Compounds for the Treatment of Cancer.

Claim Objections

Claims 1-14, 22-42, and 44 are objected to for containing elected and non-elected subject matter. The elected subject matter have been identified supra.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-14, 22-42, and 44 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of certain cancers, does not reasonably provide enablement for all cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention is the treatment of disorders associated with VERGF2 activity (Claims 9-12, 27-42), CDK2 or CDK4 activity (Claims 9-10, 13-14, 44) and the treatment of cancer (Claims 9-14, 22-42, and 44).

The State of the Prior Art and the Predictability or Lack Thereof in the Art

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:
It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Manley et al. (*Expert Opin. Investig. Drugs, 2002*, 1715-1736) teach the results of various VEGFR inhibitors in reducing certain tumors. For instance, both SU5416 and SU6668 made by Pharmacia have shown efficacy in inhibiting the growth of tumor xenografts of human melanoma, human epidermal, human prostate, human colon, human lung, rat glioma, and human glioma; while only SU6668 inhibited growth of a human ovarian cancer tumor xenograft (page 1723, last paragraph.) Combination therapies were attempted with SU5416 with cisplatin and gemcitabine and revealed a

high incidence (~ 40%) of serious thromboembolic events, vastly higher than chemotherapy (0%) or SU5416 alone (2.2%) (page 1725, second column.) Vatalanib made by Novartis and Schering AG has shown effectiveness against human prostate and epithelia carcinoma, is well tolerated in animals, and does not impair wound healing (page 1727, column 1, full paragraphs 1-2.) However, results from clinical trials of SU5416 and 6668 have been disappointing due to low efficacy and tolerability, and clinical trials of other VEGRF kinase inhibitors are in the early stages of large size clinical trials (page 1728, column 2.) Disappointing results have also raised concerns that targeting VEGF alone will be insufficient to stop tumor growth and ineffective in patients with advanced disease (page 1728, column 2, last paragraph.) Animal studies have shown that tumors may continue to grow under antiangiogenic therapy, due to a selection of more hypoxia-resistant tumor cells or by a process of vessel co-option, wherby tumor cells line up along existing blood vessels to obtain oxygen and nutrients (page 1729, column 1.) For advanced disease, antiangiogenic therapy will probably not be adequate, necessitating combinations with conventional therapies, such as cytotoxic agents and radiotherapy that directly target tumor cells (page 1729, column 1.) Also, concerns were raised due to the reported toxicity of SU5416 with cisplatin and gemcitabine (page 1729, columns 1-2.)

Davies et al. (*Pharmacology & Therapeutics, 2002*, 125-133) and Toogood (*Medicinal Research Reviews, 2001*, 487-498) both teach various inhibitors of CDK2 and CDK4, but show no data as to the usefulness of inhibiting these kinases as a treatment for cancer.

Hence, in the absence of a showing of correlation between all cancers claimed as capable of treatment by inhibiting VEGFR2, CDK2, and/or CDK4, one of skill in the art is unable to fully predict possible results from the administration of the compound of formula 1 due to the unpredictability of the role of inhibiting VEGFR2, CDK2, and/or CDK4, and the unpredictability of the ability of the compound of formula 1 to cause toxicity or any improvement in condition.

The Amount of Direction or Guidance Present and the Presence or Absence of Working Examples

The specification teaches in vitro assays done on compounds of formula I for inhibition of VEGFR2, CDK2, and CDK4 (pages 185-186.) However, no guidance or evidence is given throughout the specification that the inhibition of these kinases will treat all cancers. No guidance is given about the effects of combinations of compounds of formula I and other agents on the inhibition of VEGRF2, CDK2, and CDK4.

The Breadth of the Claims

The breadth of the claims is the treatment of all disorders associated with VERGF2 activity (Claims 9-12, 27-42), CDK2 or CDK4 activity (Claims 9-10, 13-14, 44) and the treatment of all cancers (Claims 9-14, 22-42, and 44).

The Quantity of Experimentation Needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which cancers can be treated with the compounds of the instant invention, dosages, the method of drug delivery, and any potential combination therapies.

The Level of Skill in the Art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of formula 1 for the treatment of all diseases mediated by antagonizing the VEGFR2, CDK2, and/or CDK4. As a result, necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of formula 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome deleting the claims.

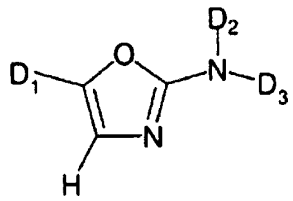
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

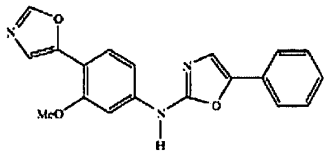
> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3 and 6-8 rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by Liu et al. (USPN 6,399,773).

The instant application claims compounds of formula I:



where: D_1 and D_2 are phenyl groups substituted as defined and all other substituents are as defined.

Liu et al. teach a compound:  which reads on the claims when D_1 is unsubstituted phenyl, D_2 is hydrogen, and D_3 is a phenyl group substituted by one C_{1-6} alkoxy and one group defined by $-(Z)_q-(Z^1)_r-(Z^2)$ where q and r are 0 and Z^2 is heteroaryl. See column 60, lines 1-31. Liu et al. also teach the pharmaceutical composition comprising the compound, a pharmaceutically acceptable carrier, and optionally other therapeutic agents. See column 31, lines 47-59.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

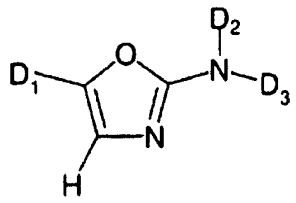
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (USPN 6,399,773).

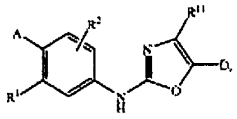
The instant application claims compounds of formula I:



where: D_1 and D_2 are phenyl groups substituted as defined and all other substituents are as defined.

Determination of the scope and content of the prior art (MPEP §2141.01)

Liu et al teach a compounds and compositions of formula VII:



with substitutions as defined. See column 9, line 35 and column 31, lines 47-59.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Liu et al. do not teach specifically all compounds which fall into the scope of the instant invention.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

Liu et al. teach generally the compounds of the instant invention where R^{11} is H, D is phenyl optionally substituted as defined and all other substitutions are as defined. See column 5, line 61, through column 9, line 65.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention was made to follow the synthetic scheme of Liu et al. and make the claimed invention with a reasonable expectation of success. The motivation to do so is provided by Liu et al. Liu et al. teach the use of the synthesized compounds

to treat inflammatory bowel disease. See column 30, line 58 through column 31, line 35.

Thus, the claimed invention as a whole was *prima facie* obviousness over the combined teachings of the prior art.

Double Patenting

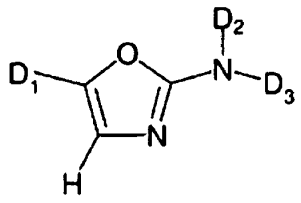
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

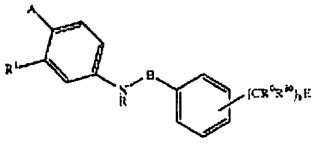
Claims 1-8 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 19, and 21 of U.S. Patent No. 6,399,773. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to the same art recognized subject matter.

The instant application claims compounds of formula I:



where: D_1 and D_2 are phenyl groups substituted as defined and all other substituents are as defined.

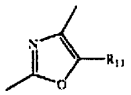
'773 teaches compounds and compositions of the formula:



with substitutions as defined.

'773 does not teach specifically all compounds which fall under the scope of the present invention.

'773 does teach generally compounds of the instant invention when B is



, R_{11} is H, and all other substituents are as defined.

Therefore, the compounds of '773 are obvious variants of the compounds of the instant application since '773 teaches some of the variations of the instant application's compounds. Hence, '773 suggests the instant invention.

Conclusion

Claims 1-14, 22-42, and 44 are rejected. Claims 1-14, 22-42, and 44 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Kosack whose telephone number is (571)-272-5575. The examiner can normally be reached on M-F 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph R Kosack

Joseph Kosack
Patent Examiner
Art Unit 1626

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER
Kamal Saeed

Joseph K. McKane
Supervisory Patent Examiner
Art Unit 1626